ACTIVATION OF SODIUM-HYDROGEN EXCHANGE IN HEART CELLS BY HYPEROSMOLAR SOLUTIONS.

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Exposure of cardiac tissue to a hyperosmolar milieu is known to increase intracellular Ca^{2+} and resting tension. This enhances cellular acid production and may therefore be expected to decrease intracellular pH (pH_i). Evidence from non-cardiac cells, however, indicates that hyperosmolality increases rather than decreases pH_i. We examined the effect of osmolality on pH_i in cardiac tissue. The resting membrane potential (E_m) of guinea pig RV papillary muscles was recorded with conventional microelectrodes; pH_i was measured with ion-sensitive microelectrodes. E_m of 6 specimens in isotonic, modified HEPES-Tyrode's solution (315 mOsm, pH 7.40 at 35° C) was 83.7 ± 1.7 mV (mean ± SE) while pH_i was 7.09 ± 0.02. E_m hyperpolarized by 2.7 ± 0.65 mV ($p<0.01$) and pH_i increased by 0.10 ± 0.03 ($p<0.02$) after switching to a similar superfusate rendered hyperosmolar (420 mOsm) with sucrose. In search of a mechanism for the alkaline shift we superfused 5 additional specimens with Tyrode's solution containing 5×10^{-5} M 5-(N,N-dimethyl)amiloride (DMA). The pH_i in DMA containing solution was 6.98 ± 0.03. E_m hyperpolarized by 3.1 ± 1.1 mV ($p<0.05$) and pH_i decreased by 0.06 ± 0.01 units ($p<0.02$) after switching to DMA-containing hyperosmolar solution. A similar response to hyperosmolality was seen when extracellular Na^+ was reduced to 15mM. We conclude that exposure to a hyperosmolar milieu causes an alkalinization within heart cells. Abolition of this response by DMA and by a reduction of extracellular Na^+ strongly suggests that it is mediated by activation of the sarcolemmal Na^+-H^+ antiport.

JUNCTIONAL ZONE BETWEEN SEGMENTS OF VARYING ACTION POTENTIAL DURATION APPEARS TO BE A SITE OF ARRHYTHMOGENESIS

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We examined activity at the junctional zone between sheep Purkinje fiber (n=15) displaying repolarization abnormalities and normal tissue in a double chamber bath using 3 standard microelectrodes. Ethylenediamine tetraacetate (3.3 mM) was added to one chamber (AEN). One microelectrode was located in AEN 3-4 mm from the junction. The other chamber, bathed in unmodified Tyrode's, had a microelectrode at the junction (NL-J) and another 3-4 mm distally in normal tissue (NL-D). At 5-10 minutes: the action potential in AEN but not in NL was prolonged. A second plateau (at -65 ± 3 mV) (n=9) or a gradually depolarizing slope resembling normal automaticity (n=6) appeared at NL-J but not at NL-D. In both instances, two phenomena occurred: 1) There were spontaneous activations originating at NL-J and conducting to NL-D as normal action potentials, and to AEN as early afterdepolarizations; 2) Triggered activity in NL-D was easily induced by early afterdepolarizations from AEN due to the depolarized state of action potential. These effects were abolished by the addition of lidocaine (10 mg/L) to NL. We conclude that electrotronic interactions at NL-J depolarize the transmembrane potential and facilitate automaticity and triggered activity. Therefore, the NL-J site acted as a pacemaker zone capable of inducing arrhythmias which were abolished by lidocaine.

Acidosis Influences ATP-Regulated K^+ Channels in Normal and Hypertrophied Left Ventricular Myocytes

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Cardiac K^+-ATP channels, activated by decreases in intracellular [ATP], may play a role in action potential shortening during ischemia. Patch-clamping was used to determine the effects of altering pH on properties of K^+-ATP channels in single endocardial myocytes isolated from normal and hypertrophied (via renal hypertension) cat LV. K^+-ATP channels of inside-out patches were bilaterally exposed to 140mM K^+ solution (pH ranging from 7.4 to 6.0; 22±1° C) in the absence of ATP. At pH 7.4, K^+-ATP channels from both normal and hypertrophied cells demonstrated similar slope conductances (~65pS) during hyperpolarization, while channels from normal cells showed greater inward rectification during strong depolarizations. 80mV depolarizations at pH 7.4 produced significantly greater outward conductance (56±4 pS, $p<0.05$) and higher open state probability (0.42 ±0.11, $p<0.02$) in the hypertrophied myocyte K^+-ATP channel relative to normals (51±2 pS and 0.29 ±0.06). Decreases in conductance and open-state probability occurred during acidosis in channels from both cell types. However, as external (intracellular) pH was lowered from 7.4 to 6.0 the absolute decreases in hypertrophy K^+-ATP open-state probability (0.33±0.10) and conductance (21±3 pS) at +80 mV were 23% and 55% greater than in normals (0.25 ±0.05 and 14±1 pS). These data show that ischemia-associated decreases in pH_i may modulate K^+-ATP channel properties and cellular action potential responses in normal and diseased myocardium.

CELLULAR ELECTRICAL UNCOUPLING, CONTRACTURE AND CONDUCTION DURING THE EARLY PHASE OF MYOCARDIAL ISCHEMIA: DISCORDANT EFFECTS OF VERAPAMIL OR HYPOCALCEMIA.

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Both verapamil (V) and hypocalcemia (low $[Ca^{2+}]_o$) diminish cardiac contractility, yet have dissimilar effects on action potential duration (APD) and the resting membrane potential (RMP). The purpose of this study was to contrast the effects of V and low $[Ca^{2+}]_o$ on the magnitude and time course of changes in electrical and mechanical properties of myocardium during the early phase of ischemia. Arterially perfused isolated rabbit papillary muscles were suspended in a H_2O-saturated atmosphere. Standard intra- and extracellular electrodes, and a piezo-resistive element were used to measure simultaneously action potential characteristics, passive electrical properties (extracellular longitudinal resistance, r_o, and the intracellular longitudinal resistance, r_i), conduction velocity (Θ), isometric twitch tension and resting tension. Three conditions were studied before and during no-flow ischemia: (1) perfusion with normal blood perfusate (n=12, extracellular ionized calcium concentration, $[Ca^{2+}]_o$= 1.0mM), (2) verapamil (0.5µM, n=14) normal blood perfusate, or (3) low $[Ca^{2+}]_o$ blood perfusate (n=9, $[Ca^{2+}]_o$=0.4mM).

Perfusion for 30min with V or a low $[Ca^{2+}]_o$ resulted in depolarization of the resting membrane potential (RMP, 3±1mV and 7±2mV, respectively), a decrease of the r_o (-15±4% and -26±7%); and an increase in Θ (4±2% and 6±2%). Neither intervention effected r_i. In contrast, V decreased (-20±6ms) and low $[Ca^{2+}]_o$ increased (37±5ms) the APD at the time of 50% of repolarization (APD_{50}). During the early phase of ischemia, V and low $[Ca^{2+}]_o$ showed discordant effects despite large pre-ischemic reductions in the isometric twitch tension (48±4% and 78±3%, respectively). After 8min of ischemia the following values and changes(Δ) relative to the pre-ischemic values were obtained: (* indicates $p<0.05$ compared to control)

	Θ(cm/s)	Δri(%)	ΔResting Tension(mN)	RMP(mV)	ΔAPD50(%)
Control	40±3	17±7	-0.08±0.2	-66±2	68±6
Verapamil	50±3*	18±13	0.02±0.06	-70±2	56±4*
Low $[Ca^{2+}]_o$	40±4	87±32*	0.20±0.09*	-58±3*	94±7*

These discordant effects of verapamil or low $[Ca^{2+}]_o$ on cellular electrical coupling and ischemic contracture during the early phase of myocardial ischemia may in part be related to cellular calcium shifts influenced by APD and RMP.